COMMENTARY

blood advances

TO THE EDITOR:

The race is on: bispecifics vs CAR T cells in B-cell lymphoma

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T-cell therapeutic approaches have come of age over the last 5 years and dramatically changed the treatment paradigm for relapsed/refractory (R/R) indolent and aggressive B-cell lymphomas. This consists of bispecific T-cell engaging antibodies (BiAbs) and autologous, ex vivo, expanded T cells with a chimeric antigen receptor (CAR T). Both of these therapies result in target cell lysis independent of T-cell receptor specificity and major histocompatibility complex presentation of a tumor antigen.[1] BiAbs combine the antigen binding regions from 2 different single chain antigen binding domains to form an antibody construct binding, with one arm to a surface antigen on B cells, for example CD20, and the second arm to an activating component of the T-cell receptor, CD3, causing cytotoxic T-cell activation and lysis.

Tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), and lisocabtagene maraleucel (liso-cel) are the 3 CAR-T therapies currently approved in the United States and Europe to treat adult patients with R/R large B-cell lymphoma (LBCL).[2-4] In addition, axi-cel and tisa-cel are approved for R/R follicular lymphoma (FL). Brexucabtagene autoleucel (brexu-cel), with an identical CAR design to axi-cel but generated using CD4 and CD8 selected T cells, is approved for R/R mantle cell lymphoma and R/R B-cell precursor acute lymphoblastic leukemia (BCP-ALL) in adults. All 4 CAR-T products are directed against the same epitope on CD19, the B-cell lineage marker, and are second generation constructs with an intracellular costimulatory region. They differ in their costimulatory domain, CD28 for axi-cel and brexu-cel, responsible for early, rapid expansion with limited long-term persistence and 4-1BB for tisa-cel and liso-cel responsible for greater long-term CAR-T persistence. The degree to which the CAR-T construct affects clinical efficacy and toxicity outcomes remains unclear.[5]

Besides blinatumomab, a CD19-directed T-cell engager approved for minimal residual disease positive and R/R BCP-ALL, mosunetuzumab and teclistamab are the only bispecific antibody constructs approved for patients with R/R FL and R/R multiple myeloma, respectively. Subcutaneous epcoritamab based on the EPCORE NHL-1 trial[6] and glofitamab from the NP30179 study[7] in R/R LBCL are expected to be approved shortly with odronextamab currently progressing through phase 2 studies.[8]

Results from the pivotal phase 2 trials for the CAR-T products in LBCL along with real-world registry studies from the United States and European groups are detailed in Table 1.[2,3,9-14] ZUMA-1 has the longest follow-up over 5 years confirming durability of response with axi-cel achieving a median overall survival (OS) of 25.8 months with 5-year OS rate of 43%, whereas tisa-cel in the JULIET study had a median OS of 11.1 months.[3,15] However, cross-trial comparisons can be misleading because of differences in study designs between ZUMA-1 and JULIET trials.[5]

Both the European and US real-world evidence consistently demonstrated in nonrandomized retrospective comparisons that axi-cel is associated with higher efficacy defined by objective response rate (ORR) and complete response rate (CRR), corresponding to greater progression free survival and OS in comparison with tisa-cel. The improved efficacy with axi-cel is counterbalanced with higher rates of cytokine release syndrome (CRS), any grade immune effector cell–associated neurotoxicity syndrome (ICANS), high grade ICANS (≥ grade 3) and higher 1-and 2-year nonrelapse mortality.[10,11,14]

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Table 1. Efficacy and toxicity outcomes from pivotal phase 2 CAR-T trials compared against real world experience and phase 2 BiAb trials in R/R LBCL

	Phase 2 CAR-T trials			Real-world experience of CAR-T (axi-cel vs tisa-cel)					Phase 2 expansion BiAb Trials		
	ZUMA-1 (axi-cel)[2]	JULIET (tisa-cel)[3]	TRANSCEND NHL 001 (liso-cel)[9]	UK[10]	German GLA DRST registry[11]	Spanish[12]	French DESCAR-T[13*]	US CAR-T consortium[14]	Epcoritamab[6]	Glofitamab[7]	Odronextamab[8]
Median age (y)	58	56	63	57 vs 63.5	60 vs 61	59 vs 62	62 vs 64	59 vs 67	68	66	67
Median vein-to-vein time	17 days	NR	37 days	40 days vs 50 days	35 days vs 55 days	41 days vs 52 days	NA	28 days vs 45 days		Not applicable	
ORR/CRR	82%/58%	52%/40%	73%/53%	44%/40% vs 32%/32%	74%/42% vs 53%/ 32%	60%/42% vs 54%/19%	80%/60% vs 66%/42%	52%/44% vs 41%/ 35%	63%/39%	52%/39%	53%/37%
12 mo OS/12 mo PFS	59%/44%	49%/ NR	58%/44%	57%/42% vs 44%/28%	55%/35% vs 53%/24%	51%/41% vs 47%/33%	64%/47% vs 49%/33%	62%/42% vs 59%/ 32%	NA (too short follow-up)	50%/37%	NA (too short follow-up)
Any grade CRS/ ≥grade 3	93%/13%	58%/22	42%/2%	93%/8% vs 74%/ 8%	81%/10% vs 65%/13%	88%/8% vs 73%/ 6%	86%/9% vs 76%/ 5%	85%/9% vs 39%/ 1%	50%/2.5%	63%/4%	53%/0%
Any grade ICANS/ ≥grade 3	64%/28%	21%/12%	30%/10%	44%/20% vs 15%/4%	44%/16% vs 22%/7%	42%/18% vs 16%/5%	49%/14% vs 22%/3%	56%/38% vs 11%/ 1%	6%/0.6%	8%/3%	4%/0%
NRM	3%	0%	NA	9% vs 3%	10% vs 4%	7% vs 3%	NA	12% vs 8%	0.6% (ICANS related)	0%	2%

LBCL, large B cell lymphoma; NA, not available; NR, not reported; NRM, nonrelapse mortality; PFS, progression free survival.
*The French DESCAR-T study used propensity score matching between axi-cel and tisa-cel, which might affect comparison of headline figures.

Registry studies have consistently demonstrated a higher median age for patients treated with tisa-cel, suggesting that clinicians may choose tisa-cel because of perceptions regarding toxicity.[10,11,14] Interestingly, the ZUMA-7 trial had a preplanned subgroup analysis which compared axi-cel to standard of care in patients aged >65 years that identified that axi-cel achieved CRR and event free survival outcomes similar if not greater than that in younger patients, with similar toxicity levels in the overall population.[16] Given the high efficacy and a favorable safety profile identified in the TRANSFORM trial, including median OS rate not reached with a median follow-up of 17.5 months and low CRS and ICANS rates in line with tisa-cel outcomes, liso-cel may be a preferred choice for some patients.[17] Currently, the main limitations with liso-cel include an absence of real-world evidence to confirm efficacy and safety and a more complicated manufacturing process with separate CD4 and CD8 products, which can increase the chances of out-of-specification products.

Each BiAb product developed for the LBCL setting comes with its own advantages and disadvantages with respect to administration, such as mosunetuzumab and glofitamab have fixed schedule regimens, whereas epcoritamab and odronextamab are continued until disease progression or toxicity is detected. Regular 3-week administrations until disease progression is difficult for maintaining the patients' quality of life in comparison with the one-and-done approach with CAR T. Mosunetuzumab and epcoritamab have subcutaneous formulations, which may be convenient to administer in the outpatient setting.[18]

The efficacy of the BiAbs in R/R LBCL are promising, with subcutaneous epcoritamab and IV glofitamab and odronextamab demonstrating response rates nearing those of tisa-cel in JULIET.[3,6-8] This is highlighted in Table 1 using the headline figures from the phase 2 bispecific trials in LBCL, albeit it includes some patients treated after CAR-T relapse. Longer-term data is necessary to confirm durability of response with real-world evidence needed to verify whether it proves to be a viable alternative to CAR T.

A recent phase 2 trial of fixed duration IV mosunetuzumab in R/R FL for 8 to 17 cycles based on the response demonstrated an ORR of 80% and CRR of 60%, which is comparable with an ORR of 94% and CRR of 70% with axi-cel in ZUMA-5 and an ORR of 87% and CRR of 73% with tisa-cel in the ELARA trial.[19-21] Notably, the median age of participants for all these studies at ~60 years is much younger than the real world R/R FL population. Given the follow-up is <18 months for these studies, it is not yet possible to draw conclusions comparing the durability of efficacy.

The BiAbs are potentially an alternative to CAR T in R/R disease, particularly in older patients, because they have relatively low rates of high grade (≥grade 3) CRS and ICANS, and off-the-shelf availability has convenience for use in community oncology setting. However, initial community use may remain impractical, given the incidence of grade 2 CRS events, which may necessitate hospitalization in 15% for epcoritamab, 17% for mosunetuzumab in FL, 12% for glofitamab, and 19% for odronextamab in LBCL cases.[6,7,19,22] Reassuringly, most BiAb-associated CRS events occurred in cycle 1 during step-up dosing soon after infusion, from within a few hours to the next day, with a short duration lasting from 1 to 3 days, rarely requiring intensive care unit admissions with usually no requirement for vasopressor support or high flow

oxygen.[7,19,22,23] One potential solution would be to treat patients in cell therapy centers for the first 1 or 2 cycles, followed by a transition to the community oncology to continue therapy.

A challenge is determining the order in which to treat R/R LBCL: CAR T, BiAbs, or autologous stem cell transplantation. ZUMA-7 and TRANSFORM, using axi-cel and liso-cel, respectively, found that CAR-T therapy is superior to autologous stem cell transplantation at the first relapse of LBCL in response rates and long-term survival.[24,25] The BELINDA trial found tisa-cel to be equivalent to autologous stem cell transplantation in this setting, but there were concerns about the methodology of all 3 trials that make comparison difficult.[26,27] There are limited data on the sequencing of BiAbs after CAR T for relapsed disease and vice-versa. In the BiAb trials, 11% of patients with R/R LBCL were treated with epcoritamab, 40% with odronextamab, 12% with mosunetuzumab, and 33% with glofitamab after CAR-T relapse. Reassuringly, these patients showed similar responses to patients with no prior CAR-T exposure.[6,7,22,28] The reverse may be true with BiAbs used as a line of therapy before CAR T, given that they target different tumor associated antigen, CD20 for BiAbs and CD19 for CAR-T cells. This approach has recently been described by the French LYSA group, and more evidence is expected in the future as BiAbs will be used as earlier lines of therapy.[29]

The case for BiAbs as an alternative to CAR-T therapy in R/R lymphoma is compelling, given less frequent toxicity and the capacity to manufacture to scale an off-the-shelf product, thus, providing rapid access. However, the survival data with BiAbs remain immature in comparison with those of CAR-T therapy, which has a wealth of evidence proving durability in the ~40% of patients expected to have a long-term cure.

Perhaps the question of greatest interest is how to determine the order in which to sequence these therapies. The durability of CAR T in comparison to immature survival data with BiAbs currently favors a CAR T first followed by BiAbs for progressive disease. Given the modest efficacy of standard frontline chemoimmunotherapy for LBCL and FL, the sequencing question is best answered by using prognostic tools and identifying patients at high risk of relapse and then offering them CAR T or BiAbs at an earlier line of therapy. An example of this approach was applied in the ZUMA-12 trial in which axi-cel was used at interim therapy response in the first line setting resulting in excellent outcomes.[30] Similarly, there is a great deal of interest with multiple studies combining BiAbs with conventional chemoimmunotherapy or novel therapies, such as polatuzumab, immunomodulators or Bruton's tyrosine kinase inhibitors, for earlier lines of therapy for patients who are treatment naive and in the R/R setting to improve response rates and survival. We are yet to identify the best combination approach incorporating either BiAbs or CAR T in frontline therapy for the minority of patients who are at high risk of early relapse of aggressive and indolent lymphoma. However, the promise of this future appears exciting.

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